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RELIAS MEDIA

Insulin Therapy for Type 2 Diabetes: Social, Psychological, and Clinical Factors

Initially, most people with type 2 diabetes are started on oral antidiabetic medications, but often they will need insulin therapy to maintain glycemic control because of the progressive beta-cell function decline in the pancreas. Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend that patients with type 2 diabetes should have therapy titrated and/or intensified every three months and should be started on insulin therapy within nine months after being treated with oral medications if their blood glucose levels are not at goal.[1,2]

Some studies have shown that using insulin as the initial treatment strategy for type 2 diabetes can provide a period of diabetic euglycemia or remission.[3,4] Despite the well-established clinical treatment guidelines and research findings advocating the use of insulin as the initial agent after the diagnosis, early insulin initiation or insulin intensification as recommended does not occur often enough during medical appointments. Because of its progressive nature, effective glycemic control in type 2 diabetes depends on timely initiation of insulin and the gradual increase in daily dose. Thus, clinicians are urged to emphasize the initiation and titration of insulin therapy.

Clinical inertia, defined as a lack of action on an identified clinical problem, is one factor that contributes to the initiation and titration of insulin therapy.[1] The insulin market has expanded in the last 15 years, with more insulin products made available for prescription. There are two types of human insulin (regular and NPH), four U-100 basal insulin analogs (Lantus, Basaglar, Levemir, and Tresiba), five mealtime insulin analogs (NovoLog, Humalog, Apidra, Fiasp, and Admelog), and one inhaled insulin (Afrezza). In addition, U-500 regular insulin, U-200 Tresiba, U-300 Toujeo, and U-200 Humalog are the commercially available concentrated insulin products for patients who use high doses of insulin. There are three types of pre-mixed insulin products (e.g., 70/30, 75/25, 50/50). Each of these has different pharmacokinetics, onset of action, and duration of action that clinicians must consider when optimizing the effectiveness and ensuring the safety of insulin therapy. The authors summarize the key features, characteristics, and costs of these insulin products in the Appendix available at https://bit.ly/2CaNW9q.

This article will review the psychological, social, and clinical factors pertaining to the various insulin products, as well as strategies to initiate and intensify insulin therapy, to help clinicians supplement and enhance their clinical practices in diabetes management.

Psychological and Social: Barriers to Insulin Therapy

Patient Barriers. Before a clinician initiates insulin therapy, the first step is to address patient barriers or concerns that may impede the optimization of diabetes

EXECUTIVE SUMMARY

The choices for insulin therapy are ever increasing with the development of new products that provide greater flexibility, greater range of effectiveness, lower risk of hypoglycemia, and lower pharmacokinetic and pharmacodynamic variability. These allow for individualization of treatment to match a patient's daily life but typically at greater cost.

- Multiple social and psychological barriers to effective insulin therapy exist for both patients and practitioners.
- The starting dose of basal insulin for patients with type 2 diabetes should be 0.2 to 0.3 units/kg once daily.
- It is important that the patient always take the first injection in the office. Using patient titration algorithms is more effective than waiting to titrate during office visits.

management. Some patient barriers include injection phobia, fear of being unable to prepare the correct dose of insulin for administration, the cost of insulin, the fear of side effects such as hypoglycemia and weight gain, the perception of personal failures in managing diabetes, and negative effect on social and work life.[5,6,7] Ultimately, it is the patients' decision whether to initiate insulin for the better management of their diabetes. If patients choose insulin therapy, the responsibility then falls onto the clinician to adequately address patients' concerns to ensure medication adherence.

Injection/Needle Phobia. Many patients perceive that their daily insulin injections would be painful. In fact, the size of the needle on an insulin syringe can be smaller than the size of the needle on a lancet. Demonstrating a dry injection to patients and encouraging patients to give themselves the first injection during the office visit can be very effective in overcoming this fear.[6]

Insulin Dose Preparation. Patients might be afraid that they do not have adequate skills to prepare the appropriate dose of insulin for each injection. It is crucial for clinicians to educate patients on the safe preparation of insulin to guide patients to be more self-efficacious in this process. One of the approaches is to employ a "teach-back" method by using a demonstration kit to show patients how to prepare and administer a dry injection and asking patients to repeat the process before self-managing their newly initiated insulin therapy at home. Furthermore, clinicians can refer patients to meet with a Certified Diabetes Educator (CDE), who can educate and provide feedback on injection techniques and self-management approaches.

Cost of Insulin. With the exception of generic human insulin, insulin products, mostly analogs, are very expensive, posing a financial barrier or burden on patients. Many patients are unable to afford insulin when a high co-pay is required or if they are uninsured. Clinicians can design an insulin regimen on a budget based on the patients' insulin therapy (e.g., type of insulin used and total daily dose [TDD]) by generating a list of insulin price comparison from the local pharmacies. For patients who have regimens that have been providing stable blood glucose control but who no longer can afford their brand-name insulin products (e.g., they have not reached their deductible or fall into the "donut-hole" in their Medicare Part D plans), many pharmaceutical companies offer patient assistance programs to those who meet the eligibility requirements, including individuals without insurance or with commercial insurances. (*See Table 1.*) Another strategy to address cost issues is to refer patients to local pharmacists for medication therapy management. Pharmacists can make recommendations based on patients' current medication profile to help lower the out-of-pocket expenses through suggesting pharmacotherapeutic modifications associated with de-escalating, discontinuing, and/or changing to a more cost-effective alternative. Community health workers are also great resources in the community to provide guidance in bridging the cost gaps.

Insulin Myths. Many patients link insulin with the development of diabetes-related complications because of anecdotal stories that after a person started insulin, coincidentally this person also faced the onset of a complication (e.g., chronic kidney disease or amputation). Karter et al conducted a survey study on individuals' perceptions about insulin among 169 insulin-naive or insulin-eligible type 2 diabetes patients who were starting insulin (69 nonadherent and 100 adherent).[7] Among the nonadherent patients, 35% of the participants expressed the idea that insulin could cause harm to their health. They also reported that individuals who required insulin did not take care of themselves in the past (47%) and perceived that being on insulin could cause blindness (20%), renal failure (32%), amputation (15%), stroke or myocardial infarction (19%), and early death (19%).[7]

The first step in addressing patients' concerns is to discuss their fears and the myths they have heard regarding insulin therapy and to provide evidence-based information with the goal of constructing a balanced view of risks and benefits of insulin. The next step would be to clarify that the reason for any diabetes-related complications developed is due to uncontrolled blood glucose levels and that the benefits of managing blood glucose with insulin outweigh the risks of experiencing the side effects (e.g., hypoglycemia). In addition, providers can stress that patients might not be taking insulin therapy long-term if their blood glucose levels become controlled with the therapy, and thus, de-escalating the overall pharmacotherapeutic approach is very possible by implementing lifestyle modifications. In many cases, like during hospitalization, clinicians should emphasize the effect temporary insulin therapy has on patients' blood glucose levels, leading to a reduced resistance on incorporating insulin therapy into their daily regimens at home.

Hypoglycemia and Weight Gain From Insulin Therapy. Injection pain, hypoglycemia, and weight gain are some factors that worry patients about insulin therapy. To help patients overcome these barriers, reassure them that hypoglycemic episodes are preventable. First, share with patients that there is a lower risk of hypoglycemia with the newer insulin analogs, such as rapid-acting and long-acting insulin products.[6]

Second, providers can educate patients on the signs and symptoms of hypoglycemia and actions to take when facing a hypoglycemic event. Symptoms of hypoglycemia include shaking, sweating, irritability, tachycardia, confusion, and hunger. If any of these symptoms occur, patients first should check their blood glucose levels. If the level is less than 70 mg/dL, patients should consume 15 to 20 grams of rapid-acting glucose (e.g., 3-4 glucose tablets, one-half cup of fruit juice, one-half cup of regular soda, or 1 tablespoon or 3 cubes of sugar). Fifteen minutes after glucose consumption, patients should re-check their blood glucose levels. If the level still is below 70 mg/dL, patients should repeat the hypoglycemia treatment. Once their blood glucose levels return to above 70 mg/dL, patients should consume a snack or a meal to prevent another episode of hypoglycemia.[1]

According to the 2018 ADA Standards of Medical Care for Diabetes, all patients who are at risk for clinically significant hypoglycemia, defined as a blood glucose level less than 54 mg/dL, should use a glucagon kit for managing severe hypoglycemia episodes, especially for those with type 1 diabetes.[1] Families, caregivers, and school personnel should be educated on actions to take during an episode of severe hypoglycemia, including where this medication is located as well as when and how to administer a glucagon kit.

Another barrier to initiating insulin therapy is weight gain, which can be a burden for patients who already are overweight or obese. Patients might believe that starting insulin will worsen their diabetes because of weight gain. To address this concern, reinforce that maintaining a well-balanced diet and engaging in daily physical activity are crucial for managing their diabetes, even with insulin added to intensify therapy. If patients have not started making lifestyle modifications, providers should emphasize the importance of eating a balanced meal following the modified plate method recommended by the 2018 ADA Standards of Medical Care for Diabetes. The modified plate method is a visual way to demonstrate meal planning by dividing a nine-inch plate into three sections for different food groups as well as suggesting easy-to-learn cups and bowls (four and eight ounces) to assist with measuring portion size. To create a well-balanced meal, patients should fill one-half of the plate with non-starchy vegetables (e.g., leafy green salad, green beans, broccoli), one-fourth of the plate with protein (meat, eggs, tofu), and one-fourth of the plate with carbohydrates (rice, bread, pasta). In a randomized, controlled trial, patients using the modified plate method or carbohydrate counting showed a significant HbA1c reduction over six months vs. general health education.[8] Also, clinicians can refer patients to a dietitian to initiate weight-management strategies before starting insulin.[6]

The Perception of Personal Failure. Many patients blame themselves for failing to self-manage their diabetes, despite following their treatment plans closely. One focus group investigated 87 adults with type 2 diabetes whose physicians had recommended starting insulin for six months. About 16% of participants perceived insulin initiation as the reason for their personal failure in managing their diabetes, and 14% believed that their clinicians used insulin as a threat to motivate them to keep good control of their glucose levels through lifestyle modifications and adherence to oral antidiabetic medications.[9] When a patient presents to a clinic for a follow-up appointment, clinicians should spend time explaining that starting insulin does not mean that they have failed to self-manage their diabetes. Patients need to understand that diabetes is a progressive condition, so the body does not respond to insulin the same way that it used to, thus requiring exogenous insulin to help control blood glucose levels. Insulin is the most effective way to normalize blood glucose levels, and starting insulin therapy does not necessarily mean that the patient will be on this therapy for the rest of their lives.

Inconvenience in Daily Life. Multiple insulin injections per day can be a burden for many patients, especially mealtime insulin injections requiring the patient to inject 15 to 30 minutes prior to a meal. Many patients perceive insulin as an inconvenient task because insulin potentially can compromise flexibility in their day-to-day activities, add barriers to their travels, and lead to social embarrassment when injecting insulin in a public place.

If patients are worried about giving injections in public, clinicians can design an insulin regimen that maximizes the patients' flexibility by limiting the number of daily injections. For instance, under a safe and effective circumstance, clinicians can consider starting a once-daily, long-acting insulin injection regimen. Options for mealtime insulin include insulin pens and inhalers, allowing the patient to inject/inhale their insulin quickly and discretely.[6]

Clinician Barriers. Clinicians' attitudes toward insulin therapy play a crucial role in working with patients and addressing patient concerns to better manage their diabetes. The Diabetes, Attitudes, Wishes, and Needs study of more than 3,700 nurses and healthcare providers in 13 countries examined attitudes toward insulin therapy.[10] The study authors found that 50% of healthcare providers delayed initiation of insulin until absolutely necessary. Only clinicians in Japan and India were more likely to delay prescription of insulin than American clinicians. Consequently, it is important to have strategies for clinicians to overcome any barriers that are prohibiting the provision of insulin therapy to patients.

Inadequate Time and Staff. Clinicians might hesitate to start patients on insulin because of insufficient time and personnel to educate patients on proper injection techniques and lifestyle modifications. In addition, patients' cultures, health literacy and numeracy, and psychosocial barriers all can affect the amount of time and staffing needed to properly manage patients on insulin.

Patient Anger and Adherence. The fear of patients becoming angry and nonadherent to medication can lead to clinicians' reluctance to prescribe insulin.[6] It is crucial to provide patient-centered care because, ultimately, it is the patients' responsibility to decide if they are willing to initiate and adhere to insulin.[6]

Clinicians' Knowledge. Clinicians may have a knowledge gap regarding the newer medications (e.g., GLP-1 RA, DPP-4 inhibitors) and more complex insulin dosing.[11,12] Often, physicians practicing in family and internal medicine specialities, as well as nurse practitioners and physician assistants, are comfortable prescribing longer-acting insulins and less confident in prescribing bolus insulin or premixed insulins.[13] This lack of knowledge begins early in providers' careers. In one study of internal medicine residency programs, researchers found little improvement in diabetes knowledge from the first to the last year of

residency.[14] In another study of more than 2,000 physicians, more than two-thirds believed their training was inadequate for diabetes care.[15] Since physicians with higher diabetes knowledge scores are more likely to follow clinical guidelines,[16] more training earlier in their careers is needed to improve clinicians' knowledge of diabetes management.

Overcoming Clinician Barriers. Relying on an interdisciplinary team that includes nurse CDEs and clinical pharmacists can lower the follow-up care burden placed on other clinicians. These important team members can provide patient-centered care, including titration of doses, reinforcement of proper techniques, diabetes self-management education and support (DSME/S), and education on healthy food choices.[6] Using an interdisciplinary approach can be especially helpful at new diagnosis when detailed instructions are needed on injection techniques, timing of injections, and storage.

What Are New Insulin Options and Why Do We Need Them?

New Insulins. Patients with diabetes can be very well-controlled on insulin NPH and R combination. When using these insulin formulations, the daily schedule should match the pharmacokinetics of the insulin formulations. This usually means consuming three meals each day on a fixed schedule. Furthermore, meals should be carbohydrate-consistent to prevent a hypoglycemic episode between meals and at bedtime. Some patients also might need small carbohydrate snacks to maintain their blood glucose levels. Although this regimen is effective, it requires limited to no day-to-day variability. Therefore, it can be challenging for patients to maintain and might not be realistic for most.

There is good evidence showing that new insulin products are as effective as older ones.[17] The newer insulin analogs offer reduction in the risk of insulin-related hypoglycemia, lowered pharmacokinetic and pharmacodynamic variability within an individual, enhanced insulin concentration close to human physiology, and flexibility to make insulin schedules match patients' daily routines rather than the other way around.[17] If patients happen to miss lunch, they will then skip that mealtime bolus. If they eat more than usual, they can adjust the dose of insulin before or at the meal. Furthermore, the long-acting basal insulin formulation provides better day-to-day stability and less medication-induced variability, which have been shown to reduce nocturnal hypoglycemia.[18]

How are these new insulin analogs different? Insulin molecules travel as monomers in their active form. However, insulin also can form dimers and hexamers; it is this ability to have multiple forms that allows for the different formulations with different kinetic profiles. The key pharmacologic changes made to insulin include amino acid substitution, addition of a zinc buffer, protamination, change in pH, addition of fatty acid chains, and binding to albumin.

Insulin products often are divided by their pharmacologic time profile. The categories include rapid acting, short acting, intermediate acting, and long acting.

Rapid-Acting Insulin. Rapid-acting insulin products include fast-acting insulin aspart,[19] aspart,[20] U-100 and U-200 lispro (Humalog),[21] biosimilar lispro (Admelog),[22] glulisine (Apidra),[23] and inhaled insulin technosphere (Afrezza).[24] Rapid-acting insulin analogs are best used for preventing hyperglycemia associated with meals and for acute corrections of hyperglycemia. These insulin analogs work as fast as five minutes after injection (e.g., FIASP, peak in two to four hours and can last up to four to six hours).[19] This insulin formulation typically is dosed up to 15 minutes before a meal. Some products, such as insulin aspart and insulin glulisine,[21,23] are indicated to be taken immediately following a meal. Patients who are on a basal-plus-bolus insulin regimen will need to learn how to calculate a dose for meals plus a dose for correction, which will be described below.

When patients are taking insulin for their meals and need to calculate a mealtime dose, there are a number of ways to determine the dose. These include: 1) the person ingests a fixed amount of carbohydrate to match the dose of insulin to be given; 2) insulin dosing is based on the estimated size of the meal; 3) carbohydrate counting allows a way to match the carbohydrate intake with the insulin dose through an individualized carbohydrate-to-insulin ratio. Although carbohydrate counting is recommended for many people with type 1 diabetes, the other less-intensive regimens are recommended for many people with type 2 diabetes. Many people do not like to be required to eat a fixed carbohydrate amount at each meal, but this can be a safe and effective way to dose insulin and provide a structure for a specific caloric diet that also will help with weight loss. Most of the insulin products are available in a prefilled disposable insulin pen device and a vial to use with a syringe. Rapid-acting insulin analogs are often the preferred insulin to use in insulin pumps.

The inhaled insulin technosphere formulation is the only insulin currently available for oral inhalation. It is supplied by an inhaler, and patients need to take multiple inhalations depending on the dose required. The inhalation cartridges are produced in 4, 8, and 12 units of insulin technosphere. This form of insulin affects pulmonary function, and patients should receive pulmonary function testing prior to use. Active smokers and those with chronic obstructive pulmonary disease (COPD) should not use insulin technospheres. This insulin is unique in that it has a very rapid onset of action (e.g., faster than other rapid-acting insulin products), and its duration is prolonged along the line of human R insulin.[24] A recent study in patients with type 1 diabetes comparing technosphere insulin and insulin aspart revealed that technosphere insulin with supplemental dosing at mealtimes provided enhanced postprandial blood glucose control without exposing patients to increased hypoglycemia or weight gain.[25]

Short-Acting Insulin: Human Regular (R) Insulin. Most often, short-acting insulin also is used to cover meals. Regular insulin has been available since 1982 and is available in generic versions and name brands (Humulin and Novolin).[26] This insulin is best be taken 30 minutes before a meal. Although this insulin has been available for a long time, the cost has risen substantially in the past decade. The brand name versions of these insulin formulations cost more than $100 per vial, while the ReliOn brand is available for $25 per vial. The generic version of R insulin is a great option for patients for whom cost is the primary concern. This insulin also is available for use with a disposable prefilled insulin pen. Regular insulin also is available in combination with intermediate-acting insulin.

Intermediate-Acting Insulin: Neutral Protamine Hagedorn insulin (NPH), Humulin Regular insulin (U-500). NPH is a human insulin that has been available since 1982, from the first synthetic human insulin using rDNA technology.[26] This insulin formulation has a prolonged duration compared to regular insulin because it uses a zinc buffer and protamination. It has an onset of two to four hours, peaks between six and eight hours, and can last up to 12 hours.[27,28] This insulin often is given twice daily: before breakfast, with the intent to prevent hyperglycemia associated with lunch, and before dinner, covering the periods of no oral intake between breakfast and dinner. One important feature of this insulin is the requirement that the patients eat lunch and ingest a sufficient amount of carbohydrates to match the dose of insulin taken that morning. If patients miss lunch or wait too long to eat (in terms of time after the morning NPH injection), they expose themselves to the risk of hypoglycemia. NPH is available by prefilled insulin pen and vial. Similar to R insulin, the name brand has increased substantially in price (> $100 per vial), but the ReliOn generic version can be bought for $25 per vial.

Regular insulin U-500 is provided in a super-concentrated form (500 units per mL), which leads to slightly different pharmacokinetic properties. Although the onset is similar to regular insulin U-100, the concentrated version has two peaks: The first aligns with R insulin and the second aligns with NPH, meaning the duration of this insulin is much longer and can last up to 12 hours.[29] Although the mechanism of this change in pharmacokinetics is not understood completely, this insulin often is a great option for patients who are taking large doses of insulin and who want to reduce the number of injections and the volume of each injection, which may improve absorption efficiency. U-500 regular insulin is available in 20 mL vials (10,000 units) or prefilled disposable insulin pens. The pens are metered with numerical markings to reduce the risk of dosing error. It also is recommended that if patients are using vials, they should use the special U-500 insulin syringes to reduce the risk of dosing errors, since the volume of U-500 contains five times the insulin compared to a U-100 insulin. U-500 typically is dosed two to three times per day, depending on the total daily insulin dose and the number of meals a person ingests.

Long-Acting Insulin: U-100 glargine (Lantus), U-300 glargine (Toujeo), detemir (Levemir), biosimilar glargine (Basaglar), U-100 and U-200 degludec (Tresiba). Long-acting (basal) insulin analogs are used to control blood glucose levels during the period of fasting and to suppress hepatic glucose production overnight and between meals. These insulin analogs typically are given once daily, but sometimes they are used twice daily at lower doses (< 0.4 units/kg/day) and when the volume of the injection exceeds the delivery device (pen or syringe). Insulin glargine is the first basal insulin analog and is stable for longer periods of time in the subcutaneous space with the use of amino-acid substitutions and an acidic pH. This insulin analog is now available in three glargine products: U-100 Lantus, U-300 Toujeo, and U-100 Basaglar. Insulin detemir is another long-acting basal insulin analog. It has sustained action via the use of amino acid substitution and the attachment of free fatty acid and albumin. This insulin product is not acidic and is less likely than glargine to burn on injection. Its duration is shorter than glargine, which results in the need for twice daily dosing for some people when the dose is < 0.4 units/kg.[30] Insulin degludec is a long-acting basal insulin that also uses an attachment to free fatty acids and albumin. It forms "chains of hexamers" allowing the molecule to be even more stable in the subcutaneous tissue with a resultant duration of up to 42 hours.[31] Although this insulin still is indicated for once-daily dosing, it has allowed for people to maintain adequate insulinization even with a variable dosing time.

Ryzodeg Mix 70/30 is an insulin analog that combines insulin degludec and insulin aspart. It is given subcutaneously once or twice daily before a meal.[32] This combination is available only in U-100 in a 3 mL FlexTouch pen device. Because of the long-acting component, insulin degludec has an ultra-long half-life of ~25 hours; this insulin combination matches those who have irregular schedules, leading to less than optimal adherence to injection, and who are on a basal-plus-one or basal-plus-two insulin regimen who wish to reduce the injection burden.[32] In a clinical trial comparing degludec/aspart combination and biphasic aspart in uncontrolled type 2 diabetes patients, researchers found that degludec/aspart given twice daily was more effective in reducing HbA1c levels and fasting blood glucose levels.[33] This combination also has been shown to result in fewer episodes of hypoglycemia.

The designation of units for insulin was intended to recognize the universality of the unit. For all U-100 insulin products, the same potency is intended for the same unit dose being given. It is important to note that the insulin products have different time-action profiles; for example, 20 units of a rapid-acting analog lowers the blood glucose much faster than 20 units of a long-acting analog insulin.

How Do I Use Insulin Safely and Effectively?

Insulin Conversion: From Intermediate-Acting to Long-Acting. When a clinician is switching from an intermediate-acting insulin to a long-acting insulin, the dose usually can stay the same, meaning 1:1 ratio. For example, if a patient is taking 20 units of NPH twice daily and switches to once-daily, then long-acting basal insulin is needed. Assuming the A1c is above 8% and NPH is not being used to cover meals, the clinician can switch to 40 units of once-daily glargine, levemir, or degludec. For cases in which the A1c is below 8%, dose reduction on long-acting insulin might be needed to reduce the risk of hypoglycemia after conversion. For example, the dose may need to be reduced by 10% if the A1c is less than 8% and reduced by 20% if the patient has an A1c less than 7%.[1] The same is true when converting from long-acting insulin to an intermediate-acting insulin. If a patient is switching from a long-acting basal insulin to twice or three times daily NPH, the dose usually can be equivalent if the A1c is above 8% and the patient is not experiencing hypoglycemia.

Switching From U-100 Insulin to More Concentrated Insulin Products (U-200, U-300, or U-500). Recent developments with insulin pens have made this change much easier. If the patient is using insulin pens for the insulin, the same number of units can be used safely in the switch. This is because the insulin pens change the volume of insulin given so that the units can remain the same. The one exception to this is U-500 regular insulin, which is also available in vials. In addition, special U-500 syringes are available to be used to

ensure accurate dosing of this concentrated insulin. These syringes are distinct in that they are the only insulin syringes with a green cap. All other insulin syringes have an orange cap.

Best Practices in Insulin Use, Titration, and Injection Techniques. Insulin is an important and potent treatment for type 1 and type 2 diabetes. Although many people with type 1 diabetes are treated at specialty centers, the overwhelming majority of people with type 2 diabetes are treated by primary care providers. Therefore, a working knowledge of insulin and administration, dosing, and best practices is critical for primary care physicians. Starting people on insulin can be easy, and there are some key best practices to maximize adherence and safety.

First, choose an effective starting dose. For patients with type 2 diabetes, weight-based dosing is a great way to start. Although some package inserts recommend a starting dose of 10 units, often this dose is inadequate. The American Diabetes Association recommends starting basal insulin (e.g., glargine, levemir, degludec) at 0.2 units/kg/day.[1] This dose often is strong enough that the patient will see an improvement in blood glucose levels with limited risk for hypoglycemia.

Have patients take the first shot in the office. The patients' first injection always should be given in the office under supervision. It is also important to know where patients can take insulin injections safely and that they are practicing proper injection technique. The initial dose might be used for one week to allow patients to be comfortable with dosing insulin. Once patients are comfortable with a daily injection and have experience with their response to insulin, the dose should be titrated to optimize the control of fasting blood glucose.

Let patients titrate insulin doses between visits. A number of titration schedules have been studied.[34,35,36,37] There is good evidence that the patients' blood glucose levels will be controlled quicker if they are titrating the insulin rather than having the provider lead the titration. The easiest method probably is adding one unit per day to the dose until the morning fasting glucose level is at the target recommended by clinical guidelines or set by the clinician according to patients' specific conditions/needs.[38] Another would be to adjust two to six units twice weekly to an agreed target fasting blood glucose level.[39]

Provide a projected ceiling dose for the patient to stop titrating insulin until the next appointment. Finally, it is also important that patients have perspective of how much insulin their clinician thinks they will need. When patients are started on a weight-based dose and instructed to perform self-titration based on their blood glucose levels, they may or may not appreciate that this is just the starting dose. Allowing them to know how much insulin they might need will remind them that their clinician has a plan and that the suggested small incremental increases are steps to help optimize their blood glucose safely and effectively.

Best Practices of Mealtime Doses. There are a number of ways to dose mealtime insulin, including carbohydrate counting, a fixed dose to match fixed carbohydrate intake, and an estimated dose based on the size of the meal. Each of these has a place based on the patients' type of diabetes, the patients' literacy and numeracy skills, and the economic considerations involved.

Carbohydrate Counting. Carbohydrate counting involves the concept of insulin-to-carbohydrate ratio (I:C ratio), which is a given amount of carbohydrate covered by one unit of prandial insulin. In adults, the amount of carbohydrate varies from 1 unit per 8 grams (1:8) to 1 unit per 20 grams (1:20).[40] The practice of coupling insulin with the amount of carbohydrate would lead to a more personalized and precise insulin dosing to prevent postprandial hyperglycemia, and education on integrating this concept into meal planning has been shown to improve glycemic control.[41,42,43] The benefit of carbohydrate counting is that it allows patients to take an insulin dose that matches their desired carbohydrate intake. Carbohydrate counting allows freedom in a day-to-day schedule in terms of timing and content of the meal. This insulin dosing approach can be considered for patients who are on scheduled basal and bolus insulin, who have good math skills to determine carbohydrate content of meals, who can calculate doses of insulin on the fly by taking carbohydrate content into consideration, who can calculate the differences between their current and target blood glucose levels, and who know their insulin sensitivity taking into account their immediate future activity. Rapid-acting insulin analogs are best for carbohydrate counting. Regular insulin also can be used, but timing of injections before meals should be considered. On the other hand, since patients with type 1 diabetes have little to no insulin production in the body, the insulin-to-carbohydrate ratio often is used to assist their prandial insulin dose. For patients with type 1 diabetes who might have trouble keeping up with an I:C ratio, a fixed-dose prandial insulin (e.g., small meal vs. big meal) is recommended to cover carbohydrates. In addition, ongoing education should be offered to train the patients on I:C ratio.

Fixed Insulin Dosing. For individuals who have a relatively fixed carbohydrate consumption, a fixed prandial insulin dose would be appropriate regardless of the type of diabetes.[44] Most patients with type 2 diabetes dose their mealtime insulin on a fixed-dose regimen to cover food because of their residual ability to produce endogenous insulin. This is most effective if the person maintains a relatively fixed carbohydrate intake. Although this is easy in terms of dosing, it provides less flexibility in terms of food content and schedule. This fixed insulin dose is intended to cover only the meal. If needed, patients might add extra units to correct their glycemic levels before ingesting a meal by taking into account their insulin sensitivity factor (one unit of prandial insulin lowers a certain number of mg/dL blood glucose).

Insulin Schedules. *Basal-Bolus Regimen.* The basal-bolus insulin regimen is the most intensive insulin regimen. This is best used for people with type 1 diabetes or late type 2 diabetes who no longer produce insulin endogenously. This regimen is intended to supply full insulin replacement and is the most labor intensive. People who use the basal-bolus schedule can use carbohydrate counting or fixed-meal dosing. Many people also add correction dose insulin to the mealtime dose to treat hyperglycemia preprandially.

Basal-Plus-One Dosing vs. Basal-Bolus Dosing Schedules. The basal-plus-one regimen, which is only for patients with type 2 diabetes, involves adding a dose of mealtime insulin prior to the largest meal of the day. Recent research has found that the basal-plus-one regimen is as effective as a basal-bolus regimen and may be safer. Riddle et al conducted a 60-week,

Table 1. Starting Doses for Basal Insulin Based on Specific Factors

Normal Renal Function	Impaired Renal Function	Age > 70 Years	Body Mass index < 19 kg/m²
Type 1 diabetes 0.2 units/kg/day	Type 1 or 2 diabetes eGFR 10 to 50 mL/min 0.15 units/kg/day	Type 1 or 2 diabetes 0.15 units/kg/day	Type 1 or 2 diabetes 0.15 units/kg/day
Type 2 diabetes 0.25 units/kg/day	Type 1 or 2 diabetes eGFR < 10 mL/min or end-stage renal disease 0.1 units/kg/day	Type 1 or 2 diabetes 0.15 units/kg/day	Type 1 or 2 diabetes 0.15 units/kg/day

Source: Hardee S, Tanenberg RJ. *The Diabetes Blue Book: Practical Inpatient Management of Adults With Diabetes and Hyperglycemia*. 7th ed. Rowan AG, ed. Greenville, NC: Vidant Medical Center Diabetes Program and The Brody School of Medicine at East Carolina University; 2017.

randomized trial and found that the A1c reduction was similar between basal-plus-one regimen (2.1%; $P = 0.06$) and basal-bolus combination (2.2%; $P < 0.01$).[1] When comparing to the premixed insulin group, the basal insulin regimens, regardless of the number of additional mealtime insulin doses, led to fewer episodes of hypoglycemia.[45] Davidson et al conducted another study over 24 weeks and confirmed that A1c reduction in the basal-plus-one regimen and the basal-plus-two regimen groups were non-inferior to basal-bolus combination.[46] They also found that those who were on basal-bolus combination were more likely to achieve the A1c goal of < 7% (46% of participants in this study arm) when compared to basal-plus-one regimen (30%; $P = 0.017$) and basal-plus-two regimen (33%; $P = 0.045$).[2] In terms of safety (incidence of hypoglycemia), the only statistically significant rate ratio found was in the severe hypoglycemia category between basal-plus-one regimen and basal-bolus combination ($P = 0.04$).[46] When mealtime insulin is warranted in addition to basal insulin, the ADA Standards of Care 2018 recommends starting with one dose before the biggest meal of the day and re-evaluating in three months, intensifying therapy if A1c still is not controlled optimally.[1]

Basal-Insulin-Plus-GLP-1-Receptor-Agonist Regimen. With the release of the glucagon-like peptide-1 receptor agonist (GLP-1 RA), this therapeutic agent has become a viable option for mealtime coverage. The use of a GLP-1 RA allows for prandial insulin release with a reduction in the risk of hypoglycemia.

A long-acting insulin analog with a GLP-1 RA in a fixed ratio is a novel combination therapy that was first FDA-approved in 2016 for use in adults with type 2 diabetes who were taking either agent alone but who had inadequate glycemic control. This combination is to be used as an adjunct therapy to diet and exercise.[47,48] Currently, two of these combination products available: insulin degludec (100 units/mL) and liraglutide (3.6 mg/mL) [Xultophy], and insulin glargine (100 units/mL) and lixisenatide (33 mcg/mL) [Soliqua]. Because of the GLP-1 RA component, both products carry a boxed warning for the risk of thyroid c-cell tumors and are contraindicated in patients with a history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2).[47,48]

Both products are available in a pen device with a display showing even dose steps for dosing purposes. For insulin degludec/liraglutide, the recommended starting dose is 16 dose steps with 16 units of degludec and 0.58 mg of liraglutide, and the maximum daily dose is 50 units/1.8 mg (determined by the GLP-1 RA component).[2] For insulin glargine/lixisenatide, the recommended starting dose depends on the previous long-acting insulin dose. The maximum daily dose is 60 units/20 mcg (again determined by the GLP-1 RA).[47] In terms of dose adjustments, in patients with eGFR < 15 mL/minute/1.73 m^2, insulin glargine/lixisenatide is not recommended.[47] For insulin degludec/liraglutide, no dose adjustments are recommended per manufacturer's labeling.[48] See the Appendix at https://bit.ly/2CaNW9q for a summary of these combination products, including key features and characteristics.

Both liraglutide and lixisenatide predominantly affect postprandial glucose because of their medium- or short-acting nature, respectively.[49,50,51] This combination is especially useful in obese patients because of the lower risks in weight gain and hypoglycemia events — since GLP-1 RA stimulates insulin secretion in a glucose-dependent manner — as a result of continuous intensification on insulin therapy. Limitations of this therapeutic combination include high therapeutic cost and gastrointestinal side effects (e.g., nausea).

Troubleshooting Insulin Regimens. *Common Insulin Errors.* Errors in insulin dosing can lead to adverse events, especially hypoglycemia, hypoglycemic coma, or death. Weight-based dosing can minimize the risk and can be a safe starting dose.

Basal Insulin and Total Daily Dose. This is the amount of insulin required to maintain a normal metabolic state during fasting. Initial dose and TDD are based on type of diabetes, renal function, age, and body weight to avoid hypoglycemia.[52] (*See Tables 1 and 2.*) This is especially important in elderly patients or those with chronic kidney disease or low body weight.

Typically, basal insulin (glargine, degludec, detemir) is given once daily at bedtime or in the morning. It can be given at other times of day that are convenient to the patient's schedule (note: Maintain the injection time around the same time every day ± one to two hours). Insulin detemir can be dosed once or twice daily because of its pharmacokinetics. Bolus insulin is given to match carbohydrate consumptions at meals and to correct blood glucose levels above the patient's target range. The timing of the bolus or mealtime insulin is important: 15 to 20 minutes before meals for rapid-acting insulin analogs and 30 minutes before meals for regular insulin. Blood glucose levels begin to spike with the first

Table 2. Total Daily Dose for Insulin Based on Specific Factors

Normal Renal Function	Impaired Renal Function	Age > 70 Years	Body Mass Index < 19 kg/m²
Type 1 diabetes 0.4 units/kg/day	Type 1 or 2 diabetes eGFR 10 to 50 mL/min 0.3 units/kg/day	Type 1 or 2 diabetes 0.3 units/kg/day	Type 1 or 2 diabetes 0.3 units/kg/day
Type 2 diabetes 0.5 units/kg/day	Type 1 or 2 diabetes eGFR < 10 mL/min or end-stage renal disease 0.2 units/kg/day	Type 1 or 2 diabetes 0.3 units/kg/day	Type 1 or 2 diabetes 0.3 units/kg/day

Source: Hardee S, Tanenberg RJ. *The Diabetes Blue Book: Practical Inpatient Management of Adults With Diabetes and Hyperglycemia.* 7th ed. Rowan AG, ed. Greenville, NC: Vidant Medical Center Diabetes Program and The Brody School of Medicine at East Carolina University; 2017.

Table 3. Out of Range Blood Glucose Levels and Actions for Insulin Dose Adjustment

Out of Range	What to Adjust
Fasting	Evening basal
Before lunch	Morning bolus
Before dinner	Always make sure there is an adequate basal dose. If on NPH, then look at morning dose; otherwise lunch bolus.
After meals	Bolus, exercise/physical activity, and carbohydrate consumption
Before bed	Dinner bolus and previous day's basal dose
During night	Bedtime insulin (may need to check at 2 a.m.)

bite of food, but it takes 20 to 30 minutes for the onset of insulin action. A mismatch in timing between the bolus insulin dose and meal intake can result in immediate postprandial hyperglycemia or subsequent hypoglycemia with delayed insulin action.

Once TDD is calculated, basal insulin is around 40-50% of the TDD, and mealtime insulin comprises of 50-60% of the TDD split among the three meals of the day. Remember to educate patients that mealtime insulin is to cover the carbohydrate content in a meal. For example, if a particular meal contains minimal or no carbohydrates (e.g., salad or a piece of chicken without breading), it may not require a significant amount of bolus insulin.

Adjusting Insulin Based on Blood Glucose Readings. When clinicians adjust insulin doses, it is essential to know the duration of action of the insulin, adjusting basal insulin based on fasting blood glucose levels but being cautious to avoid overbasalization. If patients' bedtime blood glucose was high, their elevated fasting blood glucose levels may reflect bedtime hyperglycemia or overnight snacking. Titrating only the basal insulin dose without addressing bedtime hyperglycemia or overnight snacks may result in fasting hypoglycemia if the bedtime blood glucose was normal or if the patient decided not to snack overnight. Table 3 shows the insulin doses to be adjusted based on the time during which blood glucose is out of range.

Overbasalization. Overbasalization occurs when HbA1c targets remain unachievable and fasting blood glucose is uncontrollable, despite up-titration of basal insulin, resulting from a lack of upper limits for basal insulin titration.[53] The pharmacokinetics of basal insulin might change with overbasalization, increasing the risk of hypoglycemia if the profile changes from peakless to an insulin peak in some patients.[53] Since there are no well-defined limits for basal insulin titration, experts recommend evaluating the need to add mealtime insulin when a basal insulin dose exceeds 0.5 unit per kilogram of body weight per day for a patient with type 2 diabetes to help with glycemic control.[54] This recommendation is supported by the 4-T Study, a type 2 diabetes trial with insulin regimens treating to A1c targets. The 4-T researchers found that by the end of year 1 (out of three years of the study duration), 82% of the participants in the basal arm would require the addition of mealtime insulin to reach the set A1c goal.[55]

Under Dosing. Although clinicians should be cautious about overbasalization, underdosing of insulin can occur. Basal insulin is titrated based on fasting blood glucose levels. If titrated appropriately by patients, insulin doses can help achieve glycemic control sooner. In reality, patients hesitate to self-titrate basal insulin dose, and many remain under-dosed until their next medical visit. Telephone follow-ups by the healthcare team could help patients get comfortable with self-titration. Patients with high insulin resistance (e.g., obesity) require much higher insulin doses, and weight-based dosing is one way to avoid underdosing apart from adding insulin sensitizers.

When to Reduce Dose. Insulin doses can vary during periods of illnesses/hospitalizations, steroid taper, and worsening of renal function. Steroids cause an increase in postprandial blood glucose levels and require higher mealtime doses. As the steroid dose is being tapered and discontinued, insulin doses may need to be titrated

down to avoid hypoglycemia. Patients with progressively worsening renal function have altered insulin pharmacokinetics and pharmacodynamics caused by decreased insulin clearance, leading to prolonged duration of insulin action and, subsequently, exposing patients to the risk of hypoglycemia if dose adjustments are not made.

Conclusion

Since so many insulin regimens are available, clinicians truly can match the insulin to their patients' lifestyles. The cost of insulin has continued to be a hurdle for many patients to access the most effective and safe insulin therapy.[56] It should be noted that the newer insulin analogs are no more potent or effective than the older human synthetic insulins; the new ones merely have time action features that allow the patients to choose a regimen to match their daily schedule. Busy clinicians should be familiar with the time action profiles of each insulin, including onset of action, peak effect, and duration of action. This will allow the best educated selection of insulin type. Further, clinicians should be able to use a weight-based algorithm to initiate basal insulin and know that patient self-titration will get the patient to goal quicker than clinician-directed titration. Once the fasting glucose is at goal, the clinician can ask the patient to evaluate the glucose excursion after meals to determine if mealtime insulin is needed. All patients taking insulin should check their blood glucose before each insulin injection, and all clinicians should assess their patients for hypoglycemia at each visit to maximize the effectiveness and ensure the safety of insulin therapy.

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CME Questions

1. What is the recommended starting dose for basal insulin for patients with type 2 diabetes?
   a. 0.1 to 0.2 unit/kg once daily
   b. 0.2 to 0.3 unit/kg once daily
   c. 0.4 to 0.5 unit/kg once daily
   d. 0.5 to 0.6 unit/kg once daily
2. A 52-year-old female reports hypoglycemia symptoms with a blood glucose of 60 mg/dL. What treatment option is recommended for this patient?
   a. Self administer a glucagon injection
   b. Consume one can of diet soda
   c. Consume one glucose tablet
   d. Consume three to four glucose tablets
3. A 55-year-old male reports having hypoglycemia around 2 p.m. daily for the previous week. He reports exercising after lunch for the past two weeks. His medication list includes detemir 20 units at night and lispro five units, 15 minutes prior to each meal. He has been watching his diet and currently follows a keto diet. What advice would you recommend to this patient?
   a. Increase the detemir from 20 to 22 units at night
   b. Exercise in the morning before breakfast
   c. Eat more carbohydrates at lunch
   d. Decrease lispro dose by two units to three units, 15 minutes prior to the meal
4. Which of the following is a possible reason a patient may be experiencing hyperglycemia prior to dinner?
   a. If taking basal dose, the dosage may be inadequate
   b. If taking a lunch bolus, the dosage may be inadequate
   c. If taking NPH, the morning dosage may be inadequate
   d. All of the above
5. Which patient would be the best candidate for regular U-500 insulin?
   a. A patient with body mass index (BMI) of 22 kg/m^2 recently diagnosed with latent autoimmune diabetes of adulthood
   b. A patient with BMI of 32 kg/m^2 who is taking glargine 40 units and glulisine 10 units each meal with A1c of 10.2
   c. A patient with a BMI of 64 kg/m^2 who is taking glargine 120 units and lispro 35 units with each meal with A1c of 9.7
   d. A patient with a BMI of 40 kg/m^2 who is taking glargine 30 units and liraglutide 1.4 mg daily with A1c of 8.5

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ABIM CME MOC ACCREDITED

Appendix: Table 1. Insulin Characteristics

Insulin	Formulations and Delivery Method	Onset of Action	Peak Effect	Duration of Action	Appearance	Administration	Co-Administration	Stability at Room Temperature (68-86° F)	Units Delivered in a Single Injection (Pens Only)	Savings and Support (Non-Government insurance)
Rapid-Acting Insulin										
Novolog (Insulin Aspart)	100 units/mL: 10 mL vial, 3 mL PenFill cartridge, 3 mL disposable Flexpen®	5 to 15 mins	30 to 90 mins	< 5 hours	Clear	SC injection within 5 to 10 mins before a meal	Can be mixed with NPH, draw Novolog into syringe first and administer immediately after mixing	Vial/pens: 28 days	1 to 80	https://www.novolog.com/type-2-diabetes/general-type-2/savings-and-coverage/cost-coverage.html
Humalog (Insulin Lispro)	100 units/mL: 10 mL vial, 3 mL vial, 3 mL Kwikpen® 3 mL cartridge 200 units/mL: 3 mL Kwikpen®				Clear	SC injection within 15 mins before a meal or immediately after a meal	Humalog U-100 can be mixed with NPH, draw U-100 into syringe first and administer immediately after mixing	Vial/pens: 28 days	100 units/mL and 200 units/mL: 1 to 60	https://www.humalog.com/u-200-kwikpen/humalog-savings-card
Apridra (Insulin Glulisine)	100 units/mL: 10 mL vial, 3 mL Solostar® pen				Clear	SC injection within 15 mins before or within 20 mins after a meal	Can be mixed with NPH, draw Apidra into syringe first and administer immediately after mixing	Vial/pens: 28 days	1 to 80	https://www.apidra.com/apidra/saving.aspx
Fiasp (Insulin Aspart)	100 units/mL: 10 mL vial, 3 mL FlexTouch® Pen, 3 mL cartridge	0 to 5 mins	1 to 3 hrs	3 to 5 hrs	Clear	SC injection up to 2 minutes before a meal or up to 20 minutes after starting the meal	Cannot be mixed with other insulins	Vial/pens: 28 days	1 to 80	
Inhaled Human Insulin										
Afrezza (Human Insulin)	Single-use cartridges: 4 units, 8 units, 12 units	5 to15 mins*	60 mins	2 to 3 hrs	Single-use cartridges			Cartridges: • Opened strips: 3 days • Sealed strips: 10 days • Inhaler: 15 days		https://www.activatethecard.com/afrezza7354/#

*Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro.
Note: All information obtained from respective product package inserts.

Appendix: Table 1. Insulin Characteristics (continued)

Insulin	Formulations and Delivery Method	Onset of Action	Peak Effect	Duration of Action	Appearance	Administration	Co-Administration	Stability at Room Temperature (68-86° F)	Units Delivered in a Single Injection (Pens Only)	Savings and Support (Non-Government insurance)
Short-Acting Insulin										
Humulin R, Novolin R, (Regular Insulin)	100 units/mL: 10 mL vial, 3 mL vial (Humulin R only)	0.5 to 1 hr	2 to 4 hrs	5 to 7 hrs	Clear	SC injection within 30 mins before a meal	Can be mixed with NPH, draw U-100 into syringe first	Humulin R: 31 days Novolin R: 42 days		Humulin: http://www.lillycares.com/aboutlillycares.aspx (need to meet all eligibility requirements)
Concentrated Regular Insulin										
Humulin R U-500	500 units/mL: 3 mL Kwikpen® and 20 mL vial	< 15 mins	0.5 to 8 hrs	13 to 24 hrs	Clear	SC injection within 30 mins before a meal	Do not mix with other insulins	Vial: 40 days Pen: 28 days	5 to 250	https://savingscard.humulin.com/?srcid=U500savings
Intermediate-Acting Insulin										
Humulin N, Novolin N (NPH)	100 units/mL: 10 mL vial, 3 mL Humulin N vial, 3 mL Humulin N Kwikpen®	2 to 4 hrs	4 to 12 hrs	12 to 18 hrs	Cloudy	SC injection as directed by physician	Can be mixed with rapid-acting insulin and regular insulin, see above for more details	Humulin N Vial: 31 days Humulin N pen: 14 days Novolin N vials: 42 days	1 to 60	Novolin N: https://www.pparx.org/prescription_assistance_programs/patient_assistance_program_insulin_novo_nordisk

Note: All information obtained from respective product package inserts.

Appendix: Table 1. Insulin Characteristics (continued)

Insulin	Formulations and Delivery Method	Onset of Action	Peak Effect	Duration of Action	Appearance	Administration	Co-Administration	Stability at Room Temperature (68-86° F)	Units Delivered in a Single Injection (Pens Only)	Savings and Support (Non-Government insurance)
Levemir (Insulin Detemir U-100) Levemir FlexTouch (Insulin Detemir U-100)	100 units/mL: 10 mL vial, 3 mL FlexTouch® pen	0.8 to 2 hrs	Relatively flat	5.7 to 23.2 hrs	Clear	SC injection given with the evening meal or at bedtime;	Do not mix with other insulins; neutral pH	Vial/pen: 42 days	1 to 80	https://www.levemir.com/savings/sign-up.html
Lantus (Insulin Glargine U-100) Lantus SoloStar (Insulin Glargine U-100)	100 units/mL: 10 mL vial, 3 mL SoloStar® pen, 3 mL cartridge	1.5 hrs	No peak	20 to 24 hrs	Clear	SC injection once daily at any time of the day, but at the same time each day	Do not mix with other insulins; acidic pH	Vial/pen: 28 days	1 to 80	https://www.lantus.com/sign-up/savings-and-support
Basaglar Kwikpen (Insulin Glargine U-100)	100 units/mL: 3 mL Kwikpen®					SC injection once daily at any time of the day, but at the same time each day	Do not mix with other insulins; acidic pH	28 days	1 to 80	https://www.basaglar.com/en/savings-support#savings
Toujeo SoloStar (Insulin Glargine U-300)	300 units/mL: 1.5 mL SoloStar® pen	6 hrs	No peak	24 hrs	Clear	SC injection once daily at any time of the day, but at the same time each day	Do not mix with other insulins; acidic pH	28 days	1 to 80	https://www.toujeo.com/toujeo-savings-card-coupon-and-support Nurse Coach Program
Tresiba FlexTouch (Insulin Degludec U-100)	100 units/ mL: 3 mL FlexTouch® pen	1 hr	No peak	42 hrs**	Clear	SC injection once daily at any time of the day	Do not mix with other insulins	56 days	1 to 80	https://www.tresiba.com/savings-and-coverage/get-instant-savings.html
Tresiba FlexTouch (Insulin degludec U-200)	200 Units/ mL: 3 mL FlexTouch® pen	1 hr	No peak	42 hrs**	Clear	SC injection once daily at any time of the day	Do not mix with other insulins	56 days	2 to 160	https://www.tresiba.com/savings-and-coverage/get-instant-savings.html

**The glucose lowering effect of Tresiba lasted at least 42 hours after the last of eight once-daily injections.
Note: All information obtained from respective product package inserts.

Appendix: Table 2. Pre-Mixed Insulin Characteristics**

Insulin	Formulations	Onset of Action	Peak Effect	Duration of Action	Appearance	Administration	Stability at Room Temperature (68-86° F)	Units Delivered in a Single Injection (Pens Only)	Savings and Support
Novolog Mix 70/30 (70% insulin aspart protamine suspension, 30% insulin aspart solution)	100 units/mL: 10 mL vials, 3 mL FlexPen®	10 to 20 mins	1.8 to 3.6 hrs	> 24 hrs	Cloudy	SC injection within 15 mins before a meal or for type 2 diabetes immediately after starting a meal	Vial: 28 days Pen: 14 days	1 to 60	https://www.novologmix70-30.com/savings-and-support/save-on-novolog-mix-70-30.html
Humalog Mix 75/25 (75% insulin lispro protamine suspension, 25% insulin lispro solution)	100 units/mL: 10 mL vials, 3 mL KwikPen®	15 to 30 mins	0.8 to 4.8 hrs	14 to 24 hrs	Cloudy	SC injection within 15 mins before a meal	Vial: 28 days KwikPen: 10 days	1 to 60	
Humalog Mix 50/50 (50% insulin lispro protamine suspension, 50% insulin lispro solution)	100 units/mL: 10 mL vials, 3 mL KwikPen®	15 to 30 mins	1 to 6.5 hrs	14 to 24 hrs	Cloudy	SC injection within 15 mins before a meal	Vial: 28 days KwikPen: 10 days	1 to 60	
Humulin 70/30, Novolin 70/30 (70% NPH, 30% regular insulin)	100 units/mL: 10 mL vials, 3 mL Humulin 70/30 vial, 3 mL Humulin 70/30 KwikPen®	Novolin: 30 mins Humulin: 30 to 90 mins	Novolin: 0.4 to 8.2 hr Humulin: 1.5 to 6.5 hrs	Humulin: 18 to 24 hrs Novolin: > 24 hrs	Cloudy	SC injection 30 to 45 mins before a meal	Humulin Vial: 31 days KwikPen: 10 days Novolin vial: 42 days	Humulin: 1 to 60	Novolin: https://www.pparx.org/prescription_assistance_programs/patient_assistance_program_insulin_novo_nordisk
Long-Acting Premixed Insulin									
Ryzodeg 70/30 FlexTouch Pen (70% Insulin degludec, 30% Insulin aspart)	100 units/mL: 3 mL FlexPen®	5 to 15 mins	1 to 2 hrs (per PI, median 72 mins)	> 24 hrs	Clear	SC injection once or twice daily with any main meal(s)	28 days	1 to 80	

** premixed insulins; do not mix with other insulins
Note: All information obtained from respective product package inserts.

Appendix: Table 3. GLP-1 RA and Insulin Combination Characteristics

Medication	Appropriate Candidates to Initiate Therapy	Initiation Dose	Titration (every 3 to 4 days)		Maximum Dose	Appearances	Stability at Room Temperature (68-86° F)	Savings and Support	Units Delivered in a Single Injection (Pens Only)	Notes
Xultophy (Insulin degludec/ liraglutide 100 units/3.6 mg/mL)	Adults with T2DM inadequately controlled on basal insulin (< 50 units daily) or liraglutide (≤ 1.8 mg daily)	16 units SC once daily	Above goal	+ 2 units	50 units SC once daily	Clear	21 days	https://www.xultophy10036.com/savings-coverage/savings-card.html	10 to 50	Administer dose at the same time each day with or without food
			Below goal	- 2 units						
Soliqua (Insulin glargine/ lixisenatide 100 units/33 mcg/mL)	Adults with T2DM inadequately controlled on basal insulin (< 60 units daily) or lixisenatide	Previously on lixisenatide or basal insulin < 30 units: 15 units SC once daily Previously on basal insulin 30 to 60 units: 30 units SC once daily	Above goal	+ 2 units	60 units SC once daily	Clear	14 days	https://www.soliqua100-33.com/hcp/soliqua-100-33-copay-savings	15 to 60	Administer once daily within an hour prior to first meal of the day
			Below goal	- 2 units						

Note: All information obtained from respective product package inserts.

Appendix: Table 4. Insulin Product Prices by Insulin Type

Insulin (Rapid Acting)	Quantity	Price ($)
Novolog Carton	5 cartridges of 3 mL	542.25
Novolog FlexPen	3 mL of 100 units/mL (5 pens)	563.47
Novolog Vial	10 mL of 100 units/mL	295.88
Apidra SoloStar Pen	3 mL of 100 units/mL (5 pens)	423.51
Apidra Vial	10 mL of 100 units/mL	196.50
Admelog SoloStar Pen	3 mL of 100 units/mL (5 pens)	456.24
Admelog Vial	10 mL of 100 units/mL	240.42
Fiasp FlexTouch	3 mL of 100 units/mL (5 pens)	563.47
Fiasp Vial	10 mL of 100 units/mL	295.88
Afrezza	Kit: 90 cartridges of 4 units	300.87
	Kit: 90 cartridges of 8 units	600.14
	Kit: 90 cartridges of 12 units	895.94
	Kit: 4-unit (30) & 8-unit (60) cartridges	460.83
	Kit: 4-unit (60) & 8-unit (30) cartridges	311.46
	Kit: 8-unit (60) & 12 unit (30) cartridges	641.75
	Titration Pack: 180 cartridges of 4 units & 8 units	895.93
	Titration Pack: 180 cartridges of 4 units, 8 units, & 12 units	1,191.73
Insulin (Short Acting)	**Quantity**	**Price ($)**
Humalog Vial	10 mL of 100 units/mL	177.87
	3 mL of 100 units/mL	88.53
Humalog KwikPen	3 mL of 100 units/mL (5 pens)	338.46
	3 mL of 200 units/mL (2 pens)	271.17
Humalog Junior KwikPen	3 mL of 100 units/mL (5 pens)	333.92
Humalog Cartridge	3 mL of 100 units/mL (5 cartridges)	515.43
Humulin R Vial	10 mL of 100 units/mL	99.38
	3 mL of 100 units/mL	48.84
Humulin R U-500 KwikPen	3 mL of 500 units/mL (2 pens)	578.73
Humulin R U-500 Vial	20 mL of 500 units/mL	1,485.14
Novolin R Vial (ReliOn)	10 mL of 100 units/mL	26.55
Insulin (Intermediate Acting)	**Quantity**	**Price ($)**
Humulin N KwikPen	3 mL of 100 units/mL (5 pens)	300.98
Humulin N Vial	10 mL of 100 units/mL	99.38
	3 mL of 100 units/mL	48.84
Novolin N Vial (ReliOn)	10 mL of 100 units/mL	26.55

Source: GoodRx. Available at: www.goodrx.com. Accessed Nov. 23, 2018.

Appendix: Table 4. Insulin Product Prices by Insulin Type (continued)

Insulin (Long Acting)	Quantity	Price ($)
Lantus SoloStar Pen	3 mL of 100 units/mL (5 pens)	280.70
Lantus Vial	10 mL of 100 units/mL	190.43
Basaglar KwikPen	3 mL of 100 units/mL (5 pens)	234.60
Levemir FlexTouch	3 mL of 100 units/mL (5 pens)	446.08
Levemir Vial	10 mL of 100 units/mL	300.00
Toujeo SoloStar Pen	1.5 mL of 300 units/mL (3 pens)	295.26
Toujeo Max	3 mL of 300 units/mL (2 pens)	501.53
Tresiba FlexTouch	3 mL of 100 units/mL (5 pens)	489.84
	3 mL of 200 units/mL (3 pens)	586.90
Insulin (Pre-Mixed)	**Quantity**	**Price ($)**
Humulin 70/30 KwikPen	3 mL of 100 units/mL (5 pens)	300.98
Humulin 70/30 Vial	3 mL of 100 units/mL	48.84
	10 mL of 100 units/mL	99.38
Novolin 70/30 Vial (ReliOn)	10 mL of 100 units/mL	26.58
Novolog 70/30 FlexPen	3 mL of 100 units/mL (5 pens)	550.86
Novolog 70/30 Vial	10 mL of 100 units/mL	292.39
Humalog 75/25 KwikPen	3 mL of 100 units/mL (5 pens)	338.47
Humalog 75/25 Vial	10 mL of 100 units/mL	184.27
Humalog 50/50 KwikPen	3 mL of 100 units/mL (5 pens)	338.47
Humalog 50/50 Vial	10 mL of 100 units/mL	184.27
Soliqua 100/33	3 mL of 100 units/mL and 33 mcg/mL (5 pens)	675.68
Xultophy 100/3.6	3 mL of 100 units/mL and 3.6 mg/mL (5 pens)	992.92

Source: GoodRx. Available at: www.goodrx.com. Accessed Nov. 23, 2018.